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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

INTERNATIONAL CONFERENCE ON HARMONIZATION

PUBLIC MEETING

Tuesday, January 21, 2003

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C O N T E N T S

P R O C E E D I N G S

Introductory Remarks

ANQUEZ: Good morning, everyone. I think we will go ahead and get started. I hope everybody got handouts around the table.

I am Christelle Anquez. I work at the Office of International Programs, Office of the Commissioner, and I am assisting Janet Showalter, the ICH coordinator for the FDA on this program. Janet was the moderator for this public meeting but, unfortunately, she was called back for a family emergency this morning. So, I will be replacing her until she comes.

I am delighted to welcome you this morning to the FDA. This is our public meeting on ICH that we routinely have before each ICH meeting. The next ICH meeting will be in February, in Tokyo.

It is really a two-purpose meeting. One, it is to give us the opportunity to provide you with an update on the topics underway in ICH and also, most of all for you, the opportunity for you to give us your input.

We will be providing an official transcript of this public meeting that will be available on the FDA website shortly. We will do a few presentations and then we will open the floor for you to ask questions and comment. If you want to ask a question, I will ask you to introduce yourself for the transcriptor.

We will start by an overview on ICH. Then we will give you the CTD implementation status and follow-up with an update on the preliminary concept paper on the clinical evaluation of QT interval prolongation. Then we will address the pharmacovigilance topics underway, and pursue that with an update on gene therapy and, lastly, Patrick, from MSSO/TRW, will give you an update on the MedDRA amendments. Justina?

ICH General Overview

MOLZON: Since Christelle is pinch-hitting for Janet I am pitch-hitting for Christelle.

I think we give this at every meeting, it is just a basic overview of how ICH works, the structure and harmonization process.

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This is basically geared for someone that has never heard about this before so I am going to flip through this quickly. If anyone in the audience has any questions, just let me know.

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ICH stands for the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use. The key here is to realize we have never agreed on how to spell harmonization. We spell it with a "z" instead of an "s" and it is the technology requirements for the registration of pharmaceuticals. So, that sort of describes the group of products it addresses, and the technology requirements are addressed via guidances.

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It is a unique approach. It is an agreement between the European Union, Japan and the United States to take action on harmonization. The unique portion of this is a joint initiative

involving regulators as well as industry as equal partners in these technical discussions. This started in 1990 and it was the first time we actually sat down with industry at a table to come up with a variety of technical guidelines. During the past twelve or thirteen years, I would dare say, our relationships have shifted. We actually get along quite well during these discussions and have accomplished quite a lot. I have always maintained that it is because of ICH that we actually ended up with PDUFA funding because everyone realized how well we could work together and accomplish common goals.

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ICH started in April, 1990 in the EFPIA offices in Brussels. It was just an idea that people had and they got together to plan an international conference. It was going to be one conference. That is why it is called the International Conference for Harmonization. One conference has now led to thirteen years of work. It established the terms of reference and method of

working.

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The objectives of ICH are to identify and eliminate the need to duplicate studies to meet different regulatory requirements. This would provide for more efficient use of resources in terms of human clinical studies, animal studies and materials. So, the result of ICH would be to save some of these resources. The bottom line is quicker access to patients of safe and effective new medicines.

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This is just a description of how ICH basically works. It is three regions and six parties. For Europe it is the European Union, the Commission and representatives from the IFPMA and EFPIA. For Japan it is the Ministry of Health, Labor and Welfare and JPMA. For the U.S., it is the FDA and PhRMA.

I should also mention that there are observers to the group. WHO has an observership. So does Canada and so does EFTA, the European Free

Trade Area. Essentially, the only country left in EFTA is Switzerland so the Swiss are also at the table.

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ICH is organized into an administrative portion and a technical portion. The administrative portion is the steering committee which involves the ICH coordinators. There is a coordinator for each region, and also the secretariat and steering committee members from each of the regions representing the various groups. I represent the Center for Drugs on the steering committee.

Then, there are technical expert working groups which tackle a variety of topics that the steering committee feels are worth the effort; can actually reach consensus. There are lots of topics that are so contentious we have never taken them up because we just figured out that we could never reach consensus. So, the steering committee sort of drives the process.

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As I already said, there are two members from each of the six parties on this ICH secretariat. The EFPIA, based in Geneva, acts as the secretariat. There are observers from Canada, EFTA and WHO.

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This is a picture of the expert working groups. The safety group deals with the preclinical topics. The efficacy group deals with the clinical topics. The quality groups would deal with the CMC topics, and regulatory communications are sort of the miscellaneous category. It is MedDRA, the electronic topics. There is an EWG for each topic with six topic leaders, one from each party. The role, of course, is do develop consensus on these technical issues.

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This is the website for CDER's guidances. CBER also has a guidance section but they are in chronological order so I have always found it sort of difficult to figure out how to find something. The guidances in CDER are grouped under ICH, under

the safety, efficacy, quality and miscellaneous section, if you are looking for copies of past guidances or new topics that are draft guidances.

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This describes the step process in ICH. So, we start with a concept paper where we build scientific consensus. When that is agreed to, it is signed off by the steering committee and released into the regions for consultation. For us, that means posting it in the Federal Register or putting a notice in the Federal Register and posting it on the CDER website. We collect the comments. We then go back in ICH and agree on a finalized document. It is adopted by the regulators, EU, Japan, U.S., Canada and Switzerland, and then it is implemented in the three regions and, for us, this means it is a guidance. This is different than what the other regions do. In the other regions it is mandatory; it is put into their legislation.

For the U.S. it is a guidance so it is not mandatory. Thankfully, even though this process

was established in 1990, it still meets our good guidance practices. There is actually a little paragraph in good guidance practices, the final rule that is published, that sort of explains how ICH fits into this. So, that was very helpful because I am not sure how we could have adapted the ICH process to meet our new requirements.

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In an effort to be transparent, there has always been a series of conferences. As I said, the very first conference was in 1991 and they thought that was going to be it; there was going to be one conference. But then, every two or three years we have another conference and the point is to share the work that has been done with the rest of the world. This is probably one of the main criticisms of ICH, that it is a closed club; it excludes these developing countries, but when it was first established there was an agreement between Japan, U.S. and Europe and that represented 95 percent of all R&D that took place, and that was in 1990.

The other thing is that that is where the R&D took place and that is also where there were strong pharmaceutical manufacturers associations. So, in order to be successful in ICH, you have to have a country with a strong R&D presence and also a strong industry. We have lots of requests from other countries to participate but they don't meet those criteria. So, we have to always explain to people, you know, how it was set up and why it is limited to the three main regions.

For the conferences we basically take turns hosting them. The first one was in Brussels. Then it was the U.S.'s turn and it was in Orlando; then Japan, Yokohama. The fourth conference was in Brussels and then it was our turn again to host in 2000 and that is when we unveiled the Common Technical Document, which I will be talking about after this. Then, a sixth conference is planned for Osaka in 2003. I believe it is in November. There are blue sheets of paper on the side announcing the next meeting.

Does anyone have any questions on just the

general ICH operations?

[No response]

CTD Implementation Status

FDA Perspective

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Now I am going to talk about the Common Technical Document. I have been giving this speech basically since November of 2000, after the topics came out of the San Diego meetings for ICH-5. I keep building and building to show the progress of the topic. When you think about it, it has only been two years since the documents were signed off and I think we have done extraordinarily well considering some of the circumstances I am going to be talking about.

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As I said, it was finalized at ICH-5, and it was November 9th through 11th in San Diego. The way this worked was that at the beginning of the week we had our ICH meetings and then the actual ICH-5 meeting was Thursday and Friday or Wednesday and Thursday, I can't remember at this point. But,

basically, three groups were working very hard, the safety, efficacy and quality groups, to get these documents finished. They were sort of in isolation. Then we threw everything on a CD and burned it for the participants to receive at the meeting.

. When we were looking at the final product we realized we had to really edit it for consistency in terms of the numbering system, the style and the format. Each of the groups had used a different system so when you put the whole document together, which is what the companies are going to be looking at, it was confusing. So, we realized this and we decided that we had a large task trying to make them consistent. But it was only when we looked at this altogether that we realized how complicated these were. When you consider that regulators have different systems, this adds another level of complexity. The truth is, no matter how closely we work together, we are still going to have some minor inconsistencies just because of the way the different systems work.

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But we want this to be the best it can be an and, as I mentioned before, my favorite inconsistency is that we never actually agreed on how to spell "harmonization." It doesn't mean we are not working towards harmonization; it is just a little, minor inconsistency.

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These complications and minor inconsistencies don't really detract from the enormous amount of work that has been done. Industry put a lot of work into this at the very beginning to convince the ICH steering committee to actually accept the topic, and everyone has just been working very, very hard and we really want the CTD to be the best it can be, as I have already said. So, we are working to do away with these ambiguities and inconsistencies and this is an evolving process.

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As an example of how the process has evolved, this was the very first triangle which is

very basic. We published this and then we realized, from a variety of meetings with DIA and other programs, that we knew that we wanted this layering effect but people were interpreting it as a silo, a stacking process. So, that was one thing that we didn't realize because we were so involved in the process. Of course, you know, if there is overview you have this layer and then you go to these summaries.

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Well, because of the meetings we have had with people, we realized that we had to be more elaborate in how we described this so we actually added some numbers to explain the process and how they are put together. You know, for a company that has a document that they have to assemble this is very important information. So, it was only after the documents came out that we realized that we had to address some of these issues, but this is an example of how the document has evolved.

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Practically, we had to work with other

regions because we couldn't just unilaterally make a decision. We couldn't decide to add the numbers and not have Europe and Japan do the same thing. So, you know, we had to work with the regions. But a lot of this experience comes with experience with the actual documents. We have basically just established a table of contents. We need to see, you know, real documents to see how this all fits together.

As I have already mentioned, meetings with industry have definitely helped in pointing out areas where we can improve. The more submissions we get in, the more familiar we will become with the documents and we will have a better idea how it all fits together. This is one of the reasons that the voluntary submission phase was extended from July, 2002 to this July of 2003. If we hadn't extended it, this would all be over and everyone would be using it but there would be, you know, rapid confusion.

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The first major source of confusion in the

CTD is it is not a "global dossier." The content is different for the U.S., the EU and Japan based on individual regulations. Some regulations have never been covered in ICH. They have been too contentious; they have never even been presented. A lot of these are chemistry topics. We have different requirements for some of the chemistry submissions. Those requirements have not changed. All the CTD is, is a common format and it is a modular presentation of summaries, reports and data. So, it is just a table of contents. So, it is a heading and different countries are going to have different amounts of information under each of those headings. So, the document in Japan, I daresay, would be the smallest of the group. It would have the same headings but a different amount of information. Then the European Union would be a little larger and then the U.S. would be larger because we are still asking for a lot more data. But the headings would all be the same. There would just be different information under those headings.

What the CTD does is incorporate the relevant ICH guidelines. There are about fifty guidelines and it incorporates the guidelines into a common structure. So, if you picture those guidelines as building blocks, all we did was arrange those guidelines in the same order, and this is what industry wanted us to do. They wanted to have a common format so they didn't have to assemble something for the European Union, disassemble it and put it back together for the U.S. and vice versa. So, all this did was to provide for a common format and industry, as I said, asked ICH to take this up. So, it was never intended to be a global dossier. It is just a common format to help with assembling the documents.

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To help with the process of helping people understand how this all fits together, the ICH has established sort of a mailbox to ask questions. It can be general questions; questions on safety, efficacy or quality. These questions are opened

right before an ICH meeting and then they are reviewed at the ICH meeting so there is a consensus opinion. It wouldn't help if each region had a different answer so we try to reach consensus answers to these questions.

The questions I am going to talk about next came out of the September meetings we had here, in Washington, D.C. The first question, number one, will a dossier using the CTD format, module 2 to 5, be identical for all regions? The answer is not necessarily.

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To elaborate on the answer, the CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions. However, the CTD does not address the content of the submissions. In terms of regional requirements, we have different requirements, as I said, for chemistry and various areas, and also the applicant's preferences. The applicant may not want to have the same indication or the same dosage form for some reason in one country versus the

other. So, the applicant has to have the flexibility to adjust the CTD to suit their needs for that market.

Some people have been brought into the ICH process late. Now the regulatory affairs people have to assemble these documents and they don't actually have an understanding of the entire purpose here and they think they should just have to do one application and give it to everybody. But that is not what this was intended to do.

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We posted a guidance, a general considerations guidance on submitting marketing applications according to the ICH CTD format back in September of 2001. It had a common period that is well over but we still encourage people to still submit things to the docket, and these meetings help with that. As people are actually working with the documents, they have real questions now. Before they were just hypothetical "what about this; what about that?" People have real questions now. We will be working on a revision to this

document which will be out, hopefully, before July of this year. We have been collecting all these comments and we have to modify the document a little bit; not a lot but just, you know, to verify some of the questions.

As an example, in module 1 we are now suggesting that the risk management plan be put into module 1. The risk management plans weren't even around in November of 2000 when the document was signed off on. So, as things have evolved, we are going to have to add things to module 1 and clarify some of the different examples.

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The general considerations document guidance basically explains what we want to be submitted. It gives a nice description of module 1 which is region specific. It generally contains labeling. I always forget the number but it is basically the form that you file; it is a lot of that information and that is the regional information. It is administrative and prescribing information. The general considerations guidance

also gives a physical description of the submission. It addresses the CTD requirements. It talks about obsolete guidances; the logistics and the time frame for a submission.

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The general considerations guidance describes the organization provided entirely on paper, but because we also have an ANDA initiative underway we didn't want companies to go backwards, so it also talks about how to adapt the CTD to our current process for electronic submissions. So, you can provide the documents electronically. This is in the PDF format. This is different than what Jon is going to be talking about, the eCTD, which is an XML process.

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We also posted the documents in the U.S. guidance format. These were posted on October 15, 2001. We kept them in the review discipline format for ease of printing and navigating. We have the safety, efficacy and quality topics. At some point down the road I think all the regions are going to

try and come up with one document top to bottom, but to help people in this transition phase we thought keeping them in the review discipline would be helpful. We actually split the safety appendices off because they were huge documents. We posted them in Word so companies could just populate the tables with data; they wouldn't have to go and recreate those.

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This is just a list of how the documents were published, and they are posted on the CDER web.

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This is the part that changes every time I give this presentation. So far, we have had eleven submissions in CTD format and we have actually had one that just came in that is not included in this. It is, I believe, the first complete CTD in paper, which is good for me because I am sitting with the medical officer and providing hands-on training. It is good for me to see what this actually looks like because up to this point all I have been doing

is reviewing CTD table of content submissions at the pre-submission meetings. So, I have never seen a real CTD, and I believe we only have one in-house right now.

So, there have been eleven submissions--twelve if you count the one that just came in--in CTD format. They have gone to seven different review divisions. All five offices, ODE one through five, have had experience. These were attempts by industry to just get their feet wet. So, there were several CTDs for new dosage forms; hybrid submissions where just the safety information was provided or just the quality information was provided. We have had paper and electronic submissions. The one that came in is a CTD for a new molecular entity. So, it is very good to have one to actually look at before the next meetings in Tokyo because amongst the regulators we talk about this so everyone has an idea of what this actually looks like because we don't actually write submissions; we receive submissions.

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Then I have just a series of examples that I will go through quickly to give you some examples of what we have received. The first one we received was on August 1 of 2001. It was just the pharmtox section submitted electronically, and this was for a fast track rolling submission. This surprised me because I thought, you know, the pharmtox had already been done a while ago. It was in a bunch of boxes perhaps and they would have to reformat it for the submission. So, I was very pleased to see that. So, we had a pharmtox section.

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This example is actually the World Health Organization. I can say that because they issued a press release. It is for an antimalarial. What they did, they used the CTD table of contents as it was before it was signed off. So, it wasn't even the final document so that is why the structure wasn't quite as was recommended but it was close. But here is the World Health Organization that has

never done an application in their life and they are stepping up to the plate to help.

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This is an example of a different dosage form to basically and ophthalmic product. The pharmtox submission was in the CTD format in both paper and electronics. Some companies are doing paper and electronic. It is interesting to see how they were submitting.

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Here is one for the chemistry section. The chemistry section was submitted on paper but the electronic sections were just in the old format. So, companies were doing whatever they felt comfortable with to submit this information. I am grateful for that because otherwise all of this would be taking place in a vacuum. We really need companies to step up to the plate and try and work through these documents so we have a better understanding of how they all fit together.

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The good news is there were no refuse to

files. These documents weren't perfect but they could be reviewed. When you think about it, we will get an application from Merck or Lilly or other companies and a reviewer will work on the Merck application for a while and get that finished quickly, and then move to the Lilly one and it is a completely different application. They are just set up completely differently. So, down time, the learning curve that is required to jump from one application, from one company to the next, is nothing more than going from reviewers who are normally seeing submissions from various companies going to the CTD. So, it is not that big a transition. The medical reviewers that I have talked to don't think this is a big deal. They just find the data and then they do what they are supposed to. So, I have not received any comment about this being way different than what they normally do; more difficult, or anything else. They can be reviewed and that is what the reviewers are used to doing.

We are being flexible during this

volunteer submission phase which lasts through July of this year. In July the CTD format will become mandatory in the European Union and Japan, and highly recommended in the U.S. It is highly recommended because these are guidances. That is the strongest wording we can use. We fully anticipate that this will be the format that the documents will be coming in, but we can't say that it is required because these documents are a guidance and not regulations and companies are having a hard time figuring this out. They say, "we don't have to do it." I say, "well, if you're going to be submitting it to the European Union, why wouldn't you do it?" So, I don't understand why some people are really hung up on this. It is what we anticipate seeing after July.

Once we get more applications in, we are going to provide further training based on practical experience. I am sitting with people in the pre-submission meetings. I talk to the companies off-line because they don't want the CTD to get bad publicity in meetings with all these

scientists at the pre-submission meetings. I also don't want to take up the time that the companies have for scientific discussion. So, I usually give some general information; I provide a copy of some of my presentations and then I talk with the CSO and the company and just make sure they understand how this works. We often do that with the electronic submissions. We just have the electronic submission people from the companies talk to our electronic submission group because you don't want to take up a lot of time in the pre-submission meetings because you only get about and hour or an hour and a half to meet with the division.

Once we get more applications in, we will have training based on practical experience. The reviewers that work on the documents are going to be the ones that are providing the training so that will just really provide much better experience because you cannot provide training about this until you have actually dealt with one because it just goes right over your head and you don't pay

attention. So, I encourage everyone to submit documents in the CTD format before July so you can get your feet wet before it is required in the EU and Japan and is highly recommended in the U.S. Up until 2003 hybrids are acceptable. After 2003, I don't believe we are going to be accepting hybrids and that will be put into the general considerations document but, because these aren't required, it still might be possible. We have to work this through.

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Based on my CTD pre-submission experience, I basically sit and go through all the tables of contents that are submitted. It is very important that the submission exactly match the Common Technical Document. In the table of contents, don't go and create different headings or a different numbering structure. Don't drop down to lower levels. You can do that in your document but not in the table of contents because the table of contents is what is matched to the XML version of the eCTD so you are doing yourself a disservice if

you are setting up a structure that will have to be redone when you go to the eCTD. So, provide all information under the CTD ICH negotiated headings and numbers; don't change them and don't create new headings or numbers.

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This was just an example where a company actually broke things down into smaller portions and changed the numbering system right in the table of contents. You can use sub-headers or bullets if you want in that table of contents if you think it would be clearer, but don't use a different numbering system. You can always use a more detailed numbering system within the document itself. So, if you picture the document being a PDF file hanging off the XML backbone and you click on that XML backbone and you open it up, you have a very detailed index or table of contents within that document but you shouldn't have more details in the main table of contents.

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This was covered, once again, in the Q&As.

If your company is thinking about doing a CTD between now and July, make sure you go over these questions and answers because they really address and clarify issues that are of common concern to everybody. You can read this later. It just has to do with the numbering system.

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If you don't have information for a section, just provide the number and header and "not applicable" or something else. One company skipped that portion and went through and renumbered everything and they had to do the whole thing over. That just sounds like something that, you know, I wouldn't even have to mention but I just mention it because someone actually did that.

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In terms of regional information, regional information is for unique regional information. It is information that doesn't have a general topic designation in module 3. You really have to adhere to the examples that are in the CTD document, especially for quality in 3.2.R.

One company took chemistry information, CMC information that was different for the U.S. than for Europe and they had 17 different regional appendices and all that information could be incorporated under, you know, a CTD heading and numbering structure. It is just that they thought it was unique for the U.S. So, essentially their whole application was in the appendix. So, don't do that. Just find a place to put it, and put it into that section. Don't put it into the regional information. I think there are three examples for regional information; just use those examples.

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The main topic for discussion at the meetings we had in Tyson's Corner in September was location, location, location. This is truly for the CTD quality. We are in the process of preparing a drug product and drug substance guidance and a lot of work and effort was spent at the meetings in September comparing our draft drug product and drug substance guidance for chemistry, manufacturing and controls information to the CTD.

The location of the information for drug substance/drug product in the CTD will actually be detailed in our draft guidances. It will have a topic and it will tell you where it goes in the CTD. So, that will help eliminate some misunderstanding. So, this has been a lot of work but I think it will be very helpful when it is finalized.

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Another thing that we worked hard on in September was we revised the organization of the Common Technical Document for registration for pharmaceuticals for human use. It is the first document that is posted in the group of ICHs. It describes the overall organization. What we did, we actually sat down and went through all of the document's numbers and section headers one at a time, and we read aloud and made sure that they are all consistent. So, all of the numbering and section headers have been edited for consistency. Then we came up with a document that provides guidance on document location and pagination. That

sort of describes the clumps of information you will be submitting. It just describes what information should be kept together, and that is called the granularity document. Then we once again worked on Q&As for each of the modules and those have been posted on the ICH web for clarification.

So, after every ICH meeting the most important thing to do is go to the ICH website, ICH.org, to get the most up to date information. It takes a while for us to get these turned into our guidances and post it but it is immediately posted, within the next week, on the ICH web. Basically, all of that information is going to be the same in the regions, it just takes us a while to put it through the guidance process.

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The final ICH CTD that was adopted is posted on the ICH web. It will take us a while to get this into our system because it is basically taking this huge document and going through it, updating little headers and sections. So, just use

the one that is on the ICH website.

We have a little disclaimer in the document now that says the wording of the core CTD may be slightly different from one region to another due to specific editing and local regulations. It does not affect the common understanding by the six parties of the CTD published on the ICH website. We have certain words that we can't use in the good guidance practice. There are different spellings; a little different wording, but that doesn't mean that there is a difference. It is just based on local regulation.

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The eCTD which Jon Clark will be talking about soon has always been six months behind the CTD. That is logical because you have to describe the structure and system before you can actually turn it into an electronic submission. The eCTD will be a transport format to be moved into an agency's review environment.

Step 4 was reached in Washington, D.C.

this past September. I would say the biggest pay-off of the eCTD is that really we are going to do away with the big controversy of A4 versus 8.5 X 11 paper. This is the most frequent question. It is the most frequent comment to the docket, that and margins, I suppose.

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The other controversy is the overviews, module 2, and the summaries and how this relates to the ISS and the ISE. The name "summary" has caused great confusion. Our ISS and ISE aren't really summaries but they are integrated analyses. They are very critical components of the safety and efficacy review and they are expected to be part of the FDA submission. Nothing in the CTD has eliminated the need to provide us with this information. We are in the process of clarifying what remains of the guideline for the format of the clinical and statistical sections of an application that was published in July of 1988. I think that is about a 160-some page document. The only portions that are still in effect are the ISS

section, which is pages 32-46, and the ISE, which is pages 28-32.

At first Dr. Temple was going to update this. Then it got wrapped up into the new PDUFA-3 risk management initiative. Part of the risk management initiative is to reevaluate how we look at safety. So, the ISS is going to be worked on by a larger group and that part will be updated. Dr. Temple is still going to have to work on the ISE because we don't think anyone is looking at that as part of the risk management initiative. So, we really didn't want to come out with another document, revising it, because of this new initiative that sort of took over. So, just keep posted.

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Basically, the information you used to put in ISS and ISE you can incorporate it into the CTD and you can do whatever you want. You can put part of it into the overview, part in the summary and then more in the efficacy module. Basically, if it fits in a section, you can do it. Some people can

be very good at describing their product. For some reason it might not be a very lengthy integrated analysis because they didn't have that many studies. So, if you can fit it into one of the smaller portions, that is fine. This is also one of the most frequently asked questions at the pre-submission meetings. So, basically you should have a plan on how this should all fit together and, based on your product, you would get an answer that another company might not because they had a different program for their study program.

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The next steps for FDA are training. We had training before the ICH-5 roll-out of the document. We want to make sure that all of our review disciplines have a chance to comment. So, we actually had a huge seminar and Dr. Bob Delap, who was still here at the time and in charge of the efficacy portion of the CTD, divided the ODEs into various groups and people had to review certain sections and provide their comments, and it was a huge seminar. The chemists dealt with it on one of

their retreats and so did the pharmtox people.

You know, we had roll-out prior to signing off to make sure that we didn't miss any major red flags. I have also met with senior project managers to provide updates after every ICH meeting. They have these CSO forums, project manager forums twice a year, and I go and talk. I think there are like 195 CSOs.

What we are waiting for now is submissions because we need to have experience. What happens is when the documents come in I get notified by the main document room. I then send an e-mail to the CSO in charge and I just tell him I would be glad to meet with them before the meetings so they have a basic understand. So, I am doing one-on-one training. Then, as soon as they get enough within a division, you know, they are training one another.

[Slide]

The CTD represents one of the most ambitious and successful international harmonization activities undertaken. It is really

the result of twelve to thirteen years of work and fifty guidances that have been worked on during that time. It will significantly reduce time and resources needed by industry to compile applications for global registration.

You might not think that now when you are re-keying your program, but eventually you are going to be establishing some very nice systems, hopefully electronic, that will make this much easier to deal with.

[Slide]

From the FDA perspective, the applications are going to be more reviewable. They are going to be more consistent from application to application. They are going to be complete and well organized because there is a common format for everybody, including the smaller companies to follow. It will be more predictable and this should lead to more consistent reviews. Several of the disciplines are actually developing templates based on the CTD so that there will be more predictable, consistent reviews coming out. This will allow for easier

analysis across applications. When these documents are electronic we are going to be able to actually go in and do an across division or across product or across class analysis.

We can't really do that now because the information comes in but it is all for one application. So, in the future we are really going to be able to look at, you know, hepatotoxicity across all classes. I just think in the future this will be very, very helpful in helping us deal with safety issues.

It also will provide for easier exchange of information, and by that I mean between regulators. We can talk with our co-regulators, our colleagues. When you think about it, if applications are going to be submitted basically at the same time to the regions, we are not going to have the luxury of waiting to see how something has performed in the European market or the Japanese market and we are really going to need international peer review. We are going to have to talk to our regulators to find out what they think

about some of these applications. There are mechanisms in the CFR that allow us to do that. It is 21 CFR 20.89 where we can share things with fellow regulators without having to go through the FOI process. Of course, the eCTD is going to help facilitate electronic submissions. The bottom line here is we will be getting better drugs to patients faster.

[Slide]

These are the languages of ICH, domo arigato; thank you; danke and merci. Danke is the Swiss. Just thanks for your attention. If you have any questions, I can answer them now. Any questions?

[No response]

Well, thank you again. Who is next? You? Christelle is going to provide you an update for Europe, Japan and Canada.

Other ICH Regions Perspective

ANQUEZ: Well, the CTD got signed in San Diego in 2000. Then, back home the regulators worked at implementing it in their own regions or

countries. That implied revising legislation or developing guidance.

[Slide]

In Europe, the Volume 2 Notice to Application got modified to include the CTD requirements, and was published in May, 2002. Also,. new templates for assessment report for the centralized procedure were edited. Lastly, the Annex I to the Directive 2001/83/EC is to be revised to reflect the CTD requirements.

In Japan, a guidance on organization of application dossier appended to new pharmaceuticals application for approval was published in June, 2001.

In Canada, a preparation of drug submissions in CTD format and templates was published in September, 2001, and also data guidelines were developed or revised.

[Slide]

What is the intended scope of the submissions in CTD format? Europe will intend to call for all product type, new chemical entities,

radiopharmaceuticals, vaccines, herbals, and so on.

In Japan, it will apply to new chemical entities and new biologics for new indications, new dosage forms, new route of administration but generics and OTC are excluded.

In Canada, it will be applied to new chemical entities, new biologics, new indications, new dosage forms, new routes of administration, generics and OTCs, then later on will be extended to all other biologics and radiopharmaceuticals.

[Slide]

It was agreed that the application in CTD format could be submitted on a voluntary basis from July, 2001 to July, 2003 then it would become mandatory in Europe and Japan starting in July, 2003, and will be highly recommended in Canada.

[Slide]

During this voluntary submission phase, the regulators agree to remain very, very flexible. In EU, mixed format will be allowed, that is, part as CTD and part as the old European format would be allowed together as long as they are not mixed

within modules. But module 1 must be provided and module 2 must be either the expert report or overview/summary specific guidance. Also, there was a problem for non-GMO environmental risk assessment data and where to place that. So, guidances on this topic were developed.

In Japan, it was agreed that an application would be accepted using a combination of the CTD and non-CTD formats, and it would be the same in Canada.

[Slide]

In the three regions, in order to facilitate the implementation of the CTD, the regulators developed a questions and answers document or are in the process of developing it, and they are usually on the website.

[Slide]

With the same aim of disseminating information about the CTD and educating both reviewers and industry about the new requirements engendered by the new format, a number of training workshops were organized in the three regions both

with industry and reviewers. They are listed.

[Slide]

In the EU, in the centralized procedure which is at the EU level, seven new submissions in full CTD format were received to date and three new applications in mixed format. Five supplemental applications were received and ten are expected in the near future. I don't have any data on the decentralized procedure at the EU member states level.

In Japan four new submissions were received so far and Canada got nine new submissions, eight supplemental and ten abbreviated ones.

[Slide]

If you need further information on the implementation in the three regions, EU, Japan and Canada, I have listed the websites. Thank you. I will now welcome Jon Clark who will do a presentation on the electronic--sorry, do you have any questions?

JERUSSI: Why did you include Canada in

your presentation?

ANQUEZ: You are right, it is not part of the core ICH sponsors but it is an observer, and has been very good at implementing guidelines and we work closely with them. So, that is why I included Canada. It is one of the three observers.

JERUSSI: That is something you have to be careful about. I see they have more applications than U.S. has or Japan. I think you have to be careful about what they are doing and that it it doesn't go outside of what the three regions are trying to do.

ANQUEZ: They really usually implementing the guidances the way they are in ICH so they don't deviate at all. They are very good. They really work closely with the three regions.

MOLZON: Most of the applications that they have received are ANDAs. So, we are actually relying on them to help us figure out how the ANDA process would progress.

ANQUEZ: Jon?

Electronic CTD

[Slide]

CLARK: I am a deputy topic leader for the M2 group working right now on the Common Technical Document in ICH. I am speaking today in place of Tim Mahoney who was the rapporteur for the M2. We have spent most of our time working on eCTD in the last couple of years and I am going to go over where our status is on everything today.

[Slide]

We will go through a description of the eCTD. It will be very brief and non-technical. We will go through the results of our September ICH M2 meeting. We will go through some interim M2 work. We had a meeting agenda put together for a couple of weeks from now, in Tokyo. We will talk about the eCTD progress that we have had.

The basic idea behind the eCTD is not simply a paper list Common Technical Document; it really is a way to break the application up into hundreds of documents and to do something that has been called a "wrap" and to wrap them into some kind of a code that would make them easy to

reassemble on the other end. The advantages that gives are basically that it gets some consistency in the way the documents are handled, and also that we update a very large document such as an application. You don't have to update large chunks of information; you can send in small pieces and update those.

We accommodate all of the modules in the Common Technical Document. We have modules 2 through 5 which are the modules that we have found harmonization on. We also include a regional module 1, which is a separate XML document to keep track of things in the same style as modules 2 through 5. So, to do an eCTD you have two tables of contents, one is for 2 through 5 and the other one is for module 1. They are both XML backbones. By that, we mean they are tables of contents. They are not very easily read by the human eye. They need to be processed through a web browser in order to be easily read and then you can add style to them as you see fit.

The actual standard will be maintained by

the ICH M2 expert working group. That was a decision we made at our last meeting, that we would actually maintain the thing as long as it needs to be maintained. We signed off on an eCTD specification. We signed off for step 4 which means that we believe it is ready for implementation. We immediately then recommended a change to it, which was for a study report specification.

There were some acknowledged weaknesses in the way that the eCTD handled full clinical studies and we signed off on step 4 with acknowledgement that we would immediately request a change that would accommodate what the FDA needs to handle those study reports.

The eCTD change control process was also initiated. We are actually going to document our change control process and we have the change control document for that.

[Slide]

Of course, we approved the eCTD specification during this time up until the

meetings that we are having next week--two weeks from now. We had a video conference to do that. We defined the questions from the Q&A document. Justina was telling you how that works. We had questions through the website and we were trying to group them together and answer those questions ahead of time so we could do a little more nuts and bolts work in Tokyo.

We did a paper review on the change control document and we started the first proposal for the M2 sub-group on study reports. We had PhRMA actually put together a small group of people to help us flesh out a proposal for handling full clinical study reports within the eCTD. We put that forward as a first proposal.

UMEN: Does the clinical study report have a formal step process?

CLARK: The question was does the clinical study report have a formal step process. One of the reasons it is going along in parallel with the change control document is because the change control procedures have now been fully fleshed out.

Virtually all the resources of the M2 group were spent in getting the eCTD finalized. So, in parallel, while we solve this problem we are having a change control document go forward. We haven't fully resolved whether the changes would go through a step process or what kind of a process it would go through. That is not fully resolved. There are parties that would like to have a full step by step process. For us to fully implement the eCTD the way we had seen fit to do we need to have it sooner than later. So, there is a little bit of a push and pull there.

[Slide]

What we plan to do in our February meeting is to finalize that change control document; try to get an agreement on the study report implementation, at least get an agreement on something that could be piloted by us so we could at least make a move on how to implement that type of system for our clinical study reports.

Finalize the Q&A document, M2 eCTD style sheet--like I was saying earlier, the eCTD as it

comes in is not easily human readable. You need to have other things to go along with it so you can actually understand what is going on. That is called a style sheet sometimes. We actually are going to have a so-called default style sheet so we are working on that.

. We are going to address change requests, any that might occur above and beyond the study report; discuss XML attributes which has to do with the way we handle multiple sources of drug substances. We add what is called an attribute to an element. It is a technical term, but the point is how do you make sure that the machinery knows that there is a second source of the same material?

Updates and regional implementations have to do with FDA's idea of how to use the backbone in its electronic document management system and the idea of how other areas might use that same thing.

[Slide]

eCTD progress--we have an eCTD viewer system project in place. Version 1 is scheduled for release in the spring of 2003. I will tell you

that I have seen operating software released that could probably, at some minimal legal level, allow us access to the application. It does have some things wrong with it in terms of efficiency for review and we have asked for some changes. So, there will be some changes made there.

There is a guidance being written. Actually, it has been written and it is undergoing certain corrections and changes along the way so that we can publish how we want you to use the backbone. If you are familiar with the XML backbone for the eCTD, it is very accommodating. In particular, it has a certain piece for every single document that repeats over and over. That piece has a lot of things in it that you wouldn't necessarily use every day. So, we will propose in the guidance what days to use which things.

I skipped one here--oh, no, that is just piloting the sample eCTDs for region one. We are doing the same thing in region one as we are doing for two through five.

Market research, we are looking at all of

the commercially available software to see where we are with our contract work versus where the rest of the world is with the same types of things, and to come up with a so-called alternative. The term is alternative, meaning that we would meet an obligation to seek out alternatives before we proceed down a path further, with more money, to finish the project we are on now. So, we are underway on that as we speak.

[Slide]

Contact information for any electronic submissions should go to the address you see above there, it is esub@cder.fda.gov. That has been out there for years and years and it is still there. That is our primary source of comments.

Justina brought up the differences between paper and electronic, and one of the things that was resolved was the A4 paper versus 8.5 X 11. I will tell you that there was a bit of confusion that came up with pagination. Whereas, virtually all of the documents we have received up till now are numbered page 1 through 10,000 or whatever

number you get to from the beginning to the end, and you might insert blank pages because you know you might make mistakes and things like that, we are dropping that concept of having everything numbered all the way through and going to the concept of we have an official backbone; we use that as our so-called tabulation. Within the tabulation, within the individual files or individual documents those objects, those files are, in fact, paginated. Any questions? Mike?

UMEN: [Not at microphone; inaudible]

CLARK: I will repeat the question. The PIM project is primarily--well, the parts that are of interest to me for comparison purposes are mainly labeling, and how to accommodate the same information in eleven different languages. We don't have that problem because our official language is English and we receive documents only in English so we already have the exact same problems they have.

What I will tell you is that our labeling is in the module 1, the regional areas, so there

was no real need to come to any large agreement on how to handle labeling because they had already agreed previously to put it in module 1.

UMEN: [Not at microphone; inaudible]

CLARK: The question is will the granularity of the label for the U.S. be considered to be the same as PIM eventually? There are projects in the U.S. to consider what to do with labeling, and some of those projects do get to that granularity but it is beyond the scope of this meeting to really discuss because it is not necessarily part of the eCTD. Richard?

POSKA: Richard Poska. I actually have a two-part question. The first one is probably more for Justina and Jon both. Are both the Office of New Drug Chemistry and the Office of Generic Drugs at the point that they can accept eCTDs now?

CLARK: For paper CTDs, the answer is yes. For new drugs, we can receive something--I hope I don't cut you off here--but for paper the answer is yes. For electronic versions of the paper that are not the official eCTD--now, everybody who didn't

quite get that, you need to raise your hand, but there is a way to do a CTD that isn't necessarily the eCTD in electronic format. What you do is you make your table of contents in PDF and you make the PDF look like the CTD and you are not using the eCTD standard but you are doing it electronically. We accept those for NDAs now. We have already accepted at least one that I have seen and gone through one. I don't know whether the ANDAs are accepting those or not. Do you, Justina?

MOLZON: To my knowledge, we haven't had an ANDA. That is why I am very interested in working with Canada because they have a similar system. I think there is actually a wraps meeting this March. We are going to try have some very practical examples, and I have asked Mike Ward, from Canada, to come to that meeting to sort of explain their experience. We have generic representatives on the CTD groups but the word hasn't gotten it out yet.

POSKA: When will the complete eCTD be acceptable to both Office of New Drugs and Office

of Generic Drugs?

CLARK: That will occur at the same time. The guidances are being set up so that they all point to the same place to get the eCTD information. When we accept them for one, we will be accepting them for both. That should occur during this year.

POSKA: What about Europe and Japan as far as accepting the official electronic submission? Do you know what their status is for accepting those?

CLARK: I can't speak from here, but I believe that they are a little bit ahead of us in accepting the eCTD spec., the SML spec. They are a little ahead of us, Europe. I don't know anything about the Japanese status.

MOLZON: They are a little slower in putting things in place. If you routinely deal with Japan for submissions you probably know their status more than we do, but there is a translation issue and some other things.

CLARK: Any more? Thank you. Who is

next?

Update on the Preliminary Concept Paper on the Clinical Evaluation of QT Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

MOLZON: Last chance for questions for Jon because he has to leave for another meeting. So, if you have another issue?

[No response]

[Slide]

What I am going to talk about is sort of an experiment that is ongoing in ICH. It is a way to incorporate guidances at a higher level into the ICH process. We actually held a DIA meeting for 620 people this past Monday and Tuesday. It was an experiment on how to have an intimate discussion with 600 people and world renown experts on this topic and then capture all those thoughts and recommendations and introduce them into the ICH process. I only have a few slides but I am going to explain basically what we are doing.

The topic that this relates to is the

The topic that this relates to is the clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. As you know, there have been several products on the market that have had problems with QT prolongation. The thinking here is that if we can actually come up with a way to figure out how much of a safety issue this is once it is on the market--you know, if this shows up after the approval or actually in the drug development process, if there was a signal generated in the animal studies, what can you do to make sure that you can continue to develop that product and not just drop it by the wayside?

[Slide]

We already have a preclinical topic related to QT prolongation and it is ICH S7B. That document is the safety pharmacology studies for assessing the potential for delayed ventricular repolarization, QT interval prolongation, by human pharmaceuticals. This topic was released for consultation under step 2 in February of this year,

and it was published by the FDA in June of this year. So, we are still collecting comments. We can't really finalize this document until it works with the clinical aspects of this topic.

[Slide]

So, to look at the clinical evaluation and how you would study this problem in humans, Canada actually was requested by parliament or, you know, the government to develop a document related to QT prolongation because they were having some problems that the other regions were, some serious side effects from some products that showed QT prolongation.

The Center for Drugs was actually working on a very similar document and we realized the value of a joint effort. We further realized the value of a harmonized ICH document. Because you have an ICH observer and an ICH partner working on a document, you might as well introduce it into the ICH arena. However, we recognized the need for expertise outside of the ICH process. We needed input from electrophysiologists, cardiologists and,

you know, some people have said that ICH doesn't really have a lot of scientific expertise. That might be true because the working group members are just members from industry or members from regulatory authorities; they are not world renowned experts on these topics. So, we recognized there was a real need to have this document looked at by world renowned experts.

So, we developed a streamlined procedure. Canada and the U.S. proposed this a couple of ICH meetings ago, I think at the meeting in Brussels, where you could jump-start the ICH process by using a draft or final document that had been developed in one of the ICH regions that would provide a very strong foundation for the development of the ICH guideline.

If you remember the five steps that I explained at the beginning of this meeting, we generally start with a concept paper and then go to a consensus document. This was jump-starting the process by having an almost finalized document, but that document is very valuable because you can

include the necessary experts outside of the ICH process.

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So, what we did to gather all this expertise was we worked with DIA and NASPE, which is the North American Society for Pacing Electrophysiology, and designed a workshop to discuss the document. We developed a preliminary concept paper which was really based on the original document that Canada had drafted. We have a QT prolongation working group, headed by Dr. Robert Temple and Dr. Douglas Throckmorton and others that have helped revise that original document. We posted the document on the website of DIA, ICH, Therapeutic Products Directory from Canada and CDER, all on the same day. So, we posted the document in November so people could read the document before the workshop this past week.

We also invited experts from NASPE. NASPE helped us round up, at the very last minute, a lot of these world renowned experts on how you read

these QT prolongation intervals and what they truly mean, to discuss the physiology, the problems, and some very excellent cardiologists that are world renowned. We also included the ICH working group at the meeting so they could hear the discussion and benefit from the recommendations and conclusions of this working group. So, this was a huge meeting. There were 620 people there. We had 30 panelists, and the ICH process just would not adapt that well to that many people that would be interested in this topic. It was also a way to open it up to as many different people that wanted to attend.

[Slide]

This was really a new paradigm. It was a different approach for all of us. It was outside the norm for guideline development within ICH, the Center for Drugs and Health Canada. It was also a different venue for DIA. They are used to having these meetings in hotels. You know, a small number of people come and present their topic and there is some discussion. This was really an academic

setting. We had it at the University of Maryland at Shady Grove because we really wanted to promote academic discussions and, because we had no idea how many people were going to attend the meeting, we had to make sure that the venue could expand or contract based on the number of people that came.

[Slide]

We also had more than twice the number of panelists; probably more than three times the number of panelists. We had thirty panelists. Several of you were at the meeting last week. We just kept changing the panelists based on the topic. We broke the document down into four or five different sections and we had people address questions that were developed specifically for that section and the world renowned experts would offer their suggestions or conclusions. Then, industry was very well prepared because they had the document; they had the questions; and they actually provided some very good insight into some of these issues also.

This was, in fact, one of the largest

meetings that DIA put on outside its DIA Euro and its annual meeting and they were just overwhelmed with the number of people that were interested in this. So, this very well could become a new way to approach things. We have a number of topics under way, such as good manufacturing practices. Our risk management topics are being dealt with in this way. So, you get a lot of people in a room. You get a lot of feedback on the issues at hand.

We also had a transcript taken by this very same transcriber we have here today. The resulting recommendations and conclusions will be incorporated into the document for ICH consideration. So, the transcript will be finished before we go into ICH. The working group will have access to what they heard because they were at the meeting. They will have the transcript so they can go back and review things. Some of the recommendations are actually being incorporated into the document. They were incorporated this weekend so that we could share it with our ICH partners before the ICH meeting that is going to be

held the week of February 3rd in Tokyo.

The result will be a harmonized approach. It is sort of jump-starting the process because the document that is presented to the ICH is much more evolved than the general concept paper, but it does take a lot of work up front to get this done. I guess the point is you have to actually figure out when you are going to be introducing something like this into the ICH, and we still have to work out some of those details. But I was very pleased with the number of people that came. I thought the discussion was amazing and I think this is going to result in a very, very strong document. Yes?

KOERNER: Do you anticipate that the revised document will be posted after the meeting or prior to the meeting?

MOLZON: Please identify yourself for the transcript.

KOERNER: Chin Koerner from Novartis.

MOLZON: The document will enter the ICH process and when it gets to step 2, step 3, it will be posted in all the regions and everyone will have

a chance to comment. Anyone else?

[No response]

Actually, now I would like to ask Min Chen and Susan Lu to come down and sit up front because we are going to be talking about pharmacovigilance topics. But, first, I think we would like to take a break. We have to put the programs into the computer so it would be a good time to take a break right now. Thank you.

[Brief recess]

ANQUEZ: Welcome. Min Chen will give us an update on the V1 topic.

Update on the Pharmacovigilance Topics

V1 Topic

CHEN: Hi.

[Slide]

For the postmarketing area, ICH didn't have a topic until recently. I think in the mid-'90s there was one, the E2C guideline, that was developed and adopted by the FDA. Last year three topics came up. They were called V1, V2 and V3. I don't know why "V" was selected as the name of the

topic. Maybe it is something about pharmacovigilance; I will accept that.

I am here to provide an update for the V1 topic. The V1 topic is actually an addendum to the E2C that was published before. The expert working group was assembled earlier, last year, because there was need for an addendum to the E2C guideline. There was a meeting in June last year in London that had the first draft. A step 2 document was reached, completed in September of 2002 in Washington, D.C. and that is what I am going to provide, the status of this addendum.

[Slide]

The ICH steering committee actually signed off the step 2 document in September and it is up to the three regional regulatory agencies to publish it for additional comments. EMEA has published for comments in September of last year. They have collected some comments from EFPIA. Japan published in November. The comments deadline is January 10. So, we haven't seen any comments yet. In the U.S., we published in the Federal

Register as a notice on December 31. The comments deadline is January 24, in one week actually--no, in a few days. If you can find them and make comments in time, that would be great. I will be collecting them for the Tokyo meeting.

[Slide]

To give you a little bit of background on V1, first we have to know what PSURs are. It is called periodic safety update reports. The present situation in the U.S. is that we adopted the ICH E2C guideline in 1997. However, the periodic reports in this kind of format have not been required yet. The draft reporting guidance, published in March of 2001, actually allows companies, through waiver requests, to submit these periodic reports in E2C format. So, in FDA we do have some experience in accepting the PSURs following the E2C guideline but the experience is limited. So, we don't have a lot to say on the V1 topic as far as detailed comments because there is nothing required in the U.S. However, in EU and Japan they are required, therefore, most of the

content in the addendum is based on the EU and Japanese experiences.

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In this document the aim was to synchronize the national birthdates, local birthdates actually, with the international birthdates, how they do it and how flexible it can be--use of the latest version of the reference safety information, company core safety information, CCSI, if it is a long version of the PSUR, you can use the latest version. If it is the shorter version, such as six months or one year, you can still use the beginning of the period of CCSI as a reference.

Submission of the executive summary as part of the PSUR is a new concept, CM-5, that we adopted because when you have volumes of information in a PSUR it is very hard to know exactly what is going on in the PSUR by first looking at some of the information. So, the introduction of the executive summary, summarizing important, or highlighting important information in

the PSUR for the reader is very helpful.

Options to submit summary bridging reports and addendum reports--these two concepts were also derived from CM-5. This will give us some more information in between submissions.

Handling of solicited reports--this topic is hot in the medical community. Although this has been specified as study reports in the U.S. guidelines, internationally, because of the solicited reports from the disease management program and other survey programs, are getting more and more so there is a need for how to handle these reports in PSURs.

The next steps to the addendum are to collect all the comments for further discussions as step 3. If we can reach step 4 in the near future, that would be up to each regulatory agency to publish as a final guideline to implement.

[Slide]

I will just give you more background about the periodic reporting requirement in the U.S. In 21 CFR 314.80 there is a reporting timeline, saying

that it should be submitted quarterly for the first three years and then annually. Upon written notice, however, FDA may extend or reestablish the cycle at different times, such as new major supplement approvals or other conditions as needed.

[Slide]

Required components in the periodic report--currently there should be a narrative summary and analysis of interval expedited reports, and FDA Form 3500 A with an index consisting of a line listing of all non-expedited reports; history of actions taken.

[Slide]

In the current draft reporting guidance about period reports four sections are specified: narrative summary and analysis; narrative discussion of actions taken; index line listing; and the forms. However, the PSUR definitely adds a lot of value to the period report content and format. We welcome that and the addendum actually helped industry to have a little bit more flexibility in how to submit this PSUR to the

different regulatory agencies. In the addendum, under the introduction, it actually provides clarifications and guidance beyond what is provided in E2C. However, it should be used with E2C.

[Slide]

Under the objectives, PSURs contain proprietary information and actually the confidentiality of some of the data needs to be addressed. This is a more comprehensive safety or risk-benefit analysis preparation document. However, this can be submitted also as a stand-alone document if there are any specific safety issues that can be analyzed as either requested by the regulatory authority or initiated by the company.

[Slide]

Under general principles, in the addendum that was developed it is still one report for one active substance, however, there can be situations when separate PSURs are submitted. Fixed combinations can be separated from a single ingredient or two or more different formulations

that are very different, such as a systemic versus a topical.

[Slide]

The international birthdate and the frequency of review and reporting can be negotiated with some additional line listings and/or summary tabulations if they have different frequency. An addendum report can be used if the time period is longer.

[Slide]

We can synchronize the national birthdates with the international birthdates. It depends on how you negotiate with the regulatory agency.

[Slide]

There are summary bridging reports that you find in the addendum. The concept is based on the CIOMS-V report. It is a concise document that integrates two or more PSURs to cover a specified period.

[Slide]

Addendum reports are also used to update the most recently completed PSUR. This is actually

requested by the regulatory authorities or initiated by the companies.

[Slide]

How or when to restart the clock, I think this has been discussed very widely among the industry. The decision should be discussed with the regulatory agency when a new clinically dissimilar indication or a new population is going to be exposed to this drug in the area; a new formulation or a new route of administration.

[Slide]

The time interval between the data lock point and the submission is specified in the E2C guideline as only 60 days. Companies complain that 60 days sometimes is not enough to make a submission. So, if there is a need, industry can request an extension or change of the submission time from the regulatory agency.

[Slide]

I mentioned safety reference information. You can use it in the beginning for a shorter period report or the latest CCSI at the end of the

period for longer a period of reports.

[Slide]

The exec. summary concept is introduced.

[Slide]

The patient exposure--we all understand, it is difficult to estimate patient exposure data because there are so many different kinds of data out there available for estimating the exposure. However, we all agree that there should be consistency in the method of calculation of the patient exposure, and try to avoid any overlapping.

[Slide]

Presentation of individual case histories is also a not quite specified section. It should contain a description and analysis of the selected cases containing new or relevant information and grouped by SOCs. However, if there are a lot of reports submitted during this period of time, there should be criteria specified for how you select the cases for presentation. There are other specifications that are listed there.

[Slide]

Lastly, the overall safety information should be discussed and analyzed according to the SOC organization structure. Related terms should be reviewed together for clinical relevance instead one term after another one so that no one can figure out what the clinical relevance of these reports is. That is it. Are there any questions?

MOLZON: Did you mention how this is going to interact with the PSUR?

CHEN: I didn't because the PSUR format is not quite yet in the U.S. Why? Because the proposed rule, the suspected adverse drug reaction, is going to require a PSUR format in the near future. In that SADR rule there are a little bit different specifications about PSURs than the current E2C specifications. Therefore, in the future when the SADR is published we can discuss more what the best way or best harmonized way to put a PSUR together.

MOLZON: And we don't want to have conflicting definitions in the document that Min is working on. So, we have been waiting for this

proposed rule for a long time because it also requires the use of MedDRA, etc. Every time there is a change in the administration, it is at the top of the pile and gets kicked back down. It could be out by March so we want to make sure that nothing we do in ICH interferes with that. So, we really have to wait to see how the document actually gets put out. There is a series of questions that are asked before a proposed rule is put out, a whole process. We are not quite sure what the final document will be until it goes completely through that regulatory process. So, we are trying to work within the ICH and the document that is coming out to make sure there is no conflicting information.

CHEN: Yes. Right now for V1 the concept content really is adding a lot of value to our current periodic report content. So, we welcome the PSUR for that and this is not final until it is final.

ANQUEZ: Susan Lu will present you with an update on the V2 topic.

V2 Topic

LU: Good afternoon. This is an update on the V2 topic and the activities associated with V2.

[Slide]

The focus of V2 is on post-approval safety management. Specifically, it is a guideline on definitions and standards for expedited reporting and good case management practices.

[Slide]

Just a little background, this topic was adopted by ICH about this time last year. The working group met previously, in June and September of last year. The FDA representatives are myself and Tim Cote. Min Chen is our back-up representative from CDER.

[Slide]

V2 is a follow-up of the existing ICH E2A guideline which deals specifically with pre-approval safety data during drug development. It is based on the contents of E2A, with considerations of how the definitions and terms can be applied to the post-approval phase of a product. The style and content will be consistent with E2A

while incorporating relevant recommendations with CIOMS-V.

[Slide]

The current status is step 1, with discussion of various topics and consensus building among the three parties. I should note that this is a work under construction so definitions and concepts that I may mention here may change during our discussions. The working group at this time is moving towards finalization of a draft in preparation for step 2.

[Slide]

These are some of the highlights of the agency's goals and comments for V2. First, while we recognize the need to harmonize with other parties, our priority is to ensure that the concepts and content are consistent with current use regulations. Second, it is important that the guideline reflects good reporting practices. Additionally, there is need for further discussion to clarify various topics and some minor editorial comments in order to streamline the document.

[Slide]

The goal of V2 is to set standards; to improve the quality of safety information and to harmonize methods for gathering and reporting safety data. This slide summarizes the four sections of the guideline. Arising from the goals set forth, the V2 develops standard definitions and terms for key aspects of post-approval safety reporting and contains standards for expedited reporting and good case management.

[Slide]

This is the introduction and it mirrors that of E2A, which is to improve the quality of safety information and to ensure uniform good reporting practices in the post-approval phase.

[Slide]

Section II starts with definitions of basic terms associated with post-approval drug safety experience, such as definitions for adverse events and adverse drug reaction. Adverse reactions which are serious and unexpected should be reported promptly. The criteria for serious and

unexpectedness is discussed. Other definitions specific to post-approval safety monitoring are addressed, as well as various sources of individual case reports. Examples of these sources would include the medical literature, Internet and post-approval studies.

[Slide]

This is just an example of one of the definitions in the guideline. The definition for an adverse event has previously been agreed upon by consensus of more than thirty collaborating centers. The WHO drug monitoring center and some minor modification was taken to accommodate the post-approval environment. So, an adverse event can, therefore, be any untoward medical occurrence that is associated with use of a medicinal product whether or not it is considered related to the product.

[Slide]

Definition of an adverse reaction--here are some definitions, the first being a well-accepted definition for ADR from the WHO

technical report. The second definition is one that is found in ICH E2A. I would anticipate that the definition of the guideline when it is finalized will closely resemble that of E2A, the second definition.

[Slide]

There are two principal criteria that control priority for documenting and reporting ADR cases, seriousness and unexpectedness. So, the concept of unexpectedness refers to events which may or may not have been previously observed and documented. In a regulatory sense, an adverse reaction is considered unexpected unless it is mentioned in the local product labeling. Furthermore, the issue of class labeling is addressed in V2 which is not addressed in the regs at this time. But what is up for consideration is a statement that class ADRs would be considered unexpected only if the product itself is implicated.

[Slide]

The traditional sources of adverse

experience information are clinical trials and spontaneous reports. The latter usually far exceeds the former in numbers and types of reports over the lifetime of the product. V2 will address various sources of individual case reports, unsolicited sources and solicited sources, as well as licensor-licensee interaction and regulatory authority sources.

[Slide]

The third section of V2 defines the standards for expedited reporting and reporting time frames. There is commonality across most countries for requirements covering expedited reporting of serious unexpected adverse reactions despite some local variations.

[Slide]

As a rule, cases of adverse drug reactions that are both serious and unexpected are subject to expedited reporting. This applies to all the sources previously outlined.

[Slide]

Section III.B. addresses reporting time

frames. All serious ADR case reports should qualify for expedited reporting and must be filed no later than 15 calendar days after first knowledge by the sponsor that the case meets minimum criteria for expedited reporting. Minimum criteria is defined as an identifiable patient, an identifiable reporting source, a suspect medicinal product and an adverse reaction.

[Slide]

Lastly, the last section of V2 deals with good case management or practices which I like to refer to as good reporting practices. Several areas are covered here, the first being assessing patient and reporter identifiability; secondly, the role of narratives; single case evaluation; follow-up information; and how to report. Any questions?

[No response]

Thank you.

ANQUEZ: Thank you, Susan. Now I will turn the floor to Stephanie Simek, who will provide you with a presentation on gene therapy.

MOLZON: While Stephanie is setting things up, as Min said, her document published late so if you have any comments, make sure you turn them in as soon as possible. We will be posting yours after this go-around. So, be aware that this is a whole new set of topics so you might need to involve, you know, some different people than the normal ICH folks for safety, efficacy and quality. We are sort of branching out here and comments are welcome.

Update on Gene Therapy

SIMEK: Thank you. What I am going to do in the next few minutes is just give you a brief summary of the September 9, 2002 ICH workshop on gene therapy that was held in Washington, D.C.

[Slide]

Before I go into some of the specifics of this meeting, I think what I will do first is just give you a brief introduction regarding the events that led to the organization of this meeting. First, in Brussels, on February, 2002 the ICH steering committee met to discuss the logistics of

having a gene therapy workshop. At this time, the steering committee members were asked for comments regarding the importance of this meeting and also for possible speakers for this workshop.

In May of 2002 there was a satellite meeting held in Tokyo on biotechnology and gene therapy products, which was sponsored by Dr. Katherine Zoon and Dr. Lincoln Zang. It was noted at this time that currently scientific principles for the regulation of gene therapy products were currently being harmonized in the three different regions.

It was agreed by members of ICH that the field of gene therapy is extremely complex and is also very rapidly evolving. They suggested that there should be a mechanism for the exchange of scientific expertise and experience among ICH partners to foster harmonization of technical requirements in this particular area.

[Slide]

At the Tokyo satellite meeting three critical points were identified as priority areas

for such exchanges. These were dose definition and standardization for gene therapy viral vectors; virus shedding and, in particular, adenovirus shedding and the effect that this shedding might have on the environment and also on people who come in contact with subjects who have been treated with these gene therapy vectors. The last topic was the potential of germ-line integration, which is a particularly important issue for vectors such as retroviruses and lentiviral vectors that are currently being used in gene therapy studies.

[Slide]

Before I go into the specifics of each of the three sessions, I just want to give a brief, quick background on this workshop. I should say first that this was the first open scientific meeting that ICH held on the subject of gene therapy.

The issues that were addressed were the three that I mentioned, with probably a little bit of a change in the last subject. One was the discussion on the utility of using an adenoviral

reference material that has already been manufactured as a collaboration between industry, the academia and the FDA. The talks focused on using this reference material to assess virus particles and infectious titer among the vectors that are used by different manufacturers.

The second issue that was discussed at the workshop was adenovirus shedding in subjects that received an adenoviral vector as part of their gene transfer clinical trial.

The last topic of the meeting was a discussion on lentiviral vectors. We chose this as a novel vector system and the meeting and the discussions were concerned about what the international scientific community considered safety issues regarding the use of this vector system in potential clinical trials.

[Slide]

What I am going to do in the next two slides is just give a brief background or summary on adenovirus reference material that was developed. I will probably refer to this reference

material as the ARM.

Now, in 1999, after the death of a subject that was enrolled in an adenovirus gene therapy trial, the NIH, FDA and the gene therapy community met many times to discuss adenoviral vector safety, toxicity and efficacy. One outcome of many of these symposia and meetings was the establishment of a working group that consisted of members from industry, academia and the FDA.

The mission of the working group was to manufacture, under full CGMPs, a wild type ad-5 type vector which was produced to be used as the reference material for all investigators doing adenoviral studies. The reason this reference material was generated was that there has always really been a general concern, shared by all investigators using adenoviral vectors, about the precision and accuracy of adenoviral titers and the determination of particle counts. The real reason for this concern is that the assays that are used to measure infectious titer or particle counts are really not very consistent among different

manufacturers. Also, it has been shown that there is a sharp threshold effect that is observed when calculating the dose toxicity curve when using these vectors. It has also been shown that higher doses of vector actually cause toxicity and the toxicity is due to the virus particle itself.

Another issue of concern that the international community had was also the level of replication competent adenovirus, or RCA, that is present in each lot of vector that is manufactured, and actually how much RCA is really safe.

[Slide]

From the discussion generated at the workshop, it was agreed that when developing a particular standard or reference material, regardless of whether it is a retrovirus, lentivirus or an adenovirus, it is important to have some insight on what can be accomplished by developing that reference material. It was clear from the presentations and discussions on the use of the ARM that its use will lead to the production of more consistent, safe and quality vectors. The

use of adenovirus reference material will also allow for comparability between both preclinical and clinical studies, and will ultimately lead to development of regulatory policy for adenoviral vectors that are used in clinical trials once we obtain enough data that has been generated from the use of this reference material.

[Slide]

The next presentation addressed the issue of adenoviral shedding. Presenters addressed the safety properties of adenoviral vector products and also the safe handling of viruses in relation to the environment and against inadvertent exposure to the environment. So, the real concern here is, is there a safety issue to the health workers that administer this vector to subjects, and also to direct family members living with subjects who have been treated with an adenovirus vector?

Based on the data that was presented, the ICH experts encouraged further collection of data from clinical studies using these vectors, but agreed that at present, based on current available

data, there was no real safety risk that had been identified.

[Slide]

Next, there were numerous presentations on the novel vector system lentiviral vectors. The presentations focused on many issues but the major one was the safe use of these vectors in clinical studies. The safety issues covered topics such as generation of replication competent lentivirus, which we call RCL. This can occur during the manufacture of these vectors, and is a potential safety concern.

Also, topics discussed what types of assays would be needed to be developed and used to ensure that no RCL would be administered to subjects getting these vectors in a clinical trial.

Another issue that was discussed was that of insertional mutagenesis with the known fact that all retroviral vectors, and lentivirus is a member of that group, can integrate into the host genome. One concern of the international community is that the vector can integrate into the genome and, in

doing so, can disrupt the function of the normal gene and that this disruption could potentially lead to cancer.

There was also a discussion on the potential of lentivirus to integrate into the germ line if oocytes or sperm cells were inadvertently infected during administration of this vector.

The remaining safety issue that was touched on was the potential for mobilization of an integrated lentivector. What I mean by this is that during the normal packaging of a virus you can take what would basically be pretty much a stripped down, non-infectious virus particle but if you were treating an HIV-positive population there is the potential of a recombinant event and this might, though there is a very small chance of this, but it might lead to recombination with the wild type HIV and then lead to a potential for a stronger or more replicated vector or virus.

[Slide]

Further presentations focused on the importance of developing appropriate assays and

controls for testing for RCL so that this would not be an issue. There were also talks on vector design and the production of safer vector systems. Lastly, there was a presentation about developing appropriate in vivo animal models to study safety issues such as the mobilization and insertional mutagenesis.

[Slide]

At the conclusion of the one-day meting the ICH discussion group agreed that investigators should begin to use this adenovirus reference material to measure virus particles and infectious titer. It was also agreed that there should be a review of the accrued data generated from the use of the ARM and that this information should be evaluated and then reported back to the group at the July Brussels meeting.

This data would, hopefully, be used to correlate safety information regarding dose-related toxicities and also the level of replication competent adenovirus that is administered to subjects. When enough data is accumulated, we will

then be able to correlate this data between different investigational trials and get some consistency.

[Slide]

Finally, the discussion group recommended that adenovirus shedding data should continue to be collected and this topic should again be revisited at a later date.

In regards to the lentiviral vector system, the group recommended that tests for RCL be developed, and they also recommended that in vivo animal models for lentivirus also be developed. The consensus was that lentiviral vectors could be used in clinical applications but their use must be based on a risk-benefit consideration.

Lastly, further discussion on these topics and more in-depth discussion on germ-line transmission was proposed for the sixth ICH meeting in Japan.

I will stop here and take any questions if anybody has them.

MOLZON: Thank you, Stephanie. I would

just like to point out that in the handout for ICH-VI, if you notice on the very bottom, there is an afternoon session on gene therapy. This is a very good example of how we are dealing with emerging topics.

Stephanie, could you just relate your experience to what a wonderful program the open session was?

SIMEK: This was my first actual experience with ICH so I came in as a novice and maybe that played a part, but what I found was that the international community was very aware, everyone was very aware of the safety issues that are out there and everyone worked very well together. We wanted very much for the ICH to accept this. Although this is a novel approach for the ICH and we are not prepared at this point to write any guidances whatsoever, I think the ICH became very aware that sometimes you have to start early on to get involved in something that is moving as rapidly as this is. So, we found the EU and the Japanese delegation, as well as the other

groups--we worked together so well that I am envisioning that this will move rapidly and, hopefully, some day we might be able, you know, to have some consensus on certain requirements.

ANQUEZ: Thank you, Stephanie. Now I am very pleased to welcome Patrick Revelle and Jim Mundell from TRW, who came on purpose to give a presentation on MedDRA maintenance.

Medical Dictionary for Regulatory Activities

REVELLE: I am going to start the presentation with just some overviews. This is the first time the MSSO has addressed a public meeting of the ICH. MSSO, for those of you who don't know, is a maintenance contract for the MedDRA terminology. It was awarded back in 1998, actually, to BBM which was then merged into TRW. Also, MSSO has an oversight panel for the management board, which is an ICH expert working group itself.

[Slide]

As far as where we are right now with the MedDRA subscriptions, MedDRA's only funding is

through subscription sale. There are about 820 subscribers worldwide. This is how they fall in the ICH regions, but you also see non-ICH regions of eight percent, which is primarily regulatory authorities in those regions.

[Slide]

A different cut is by type of company or institution. As you can see, primarily it is pharmaceuticals, biologics and the CROs that support them. This other 17 percent is made up of system software designers, as well as non-regulatory governmental agencies, and then those subscribers that did not provide us with a definition of what type of company they are.

[Slide]

MedDRA has multiple levels of subscriptions that are based on revenue of the company. When we started in 1999, we had four core levels and a basic subscription and a regulatory subscription. We then added a fifth core level for the biggest companies, as well as a software developer license. We also recently added a

sub-zero license for very small companies, and we are in the process of proposing maybe a couple more modifications to the subscription service.

[Slide]

As far as regulatory standing, right now Japan was the first to strongly recommend the use of MedDRA in 1999. They now have a mandate for the use of MedDRA that will take effect on October 1 of this year for all electronic filings.

EU also has in effect now their use of MedDRA for electronic filings. It is a mandate. They also have put out a request for all single case severe safety reports going back to 1995 for those licensed within the European Union to market. They also currently have a draft version of a mandated use of MedDRA for clinical trials, which is in internal review.

As for the United States, as of January 4, we believe it is, the proposed rule went back to OMB for review and has another 90-day review period.

[Slide]

This is just a listing of some of the regulators, not necessarily all of them, but you can see that outside of the ICH you have things like Argentina, Taiwan, Malaysia. A few months ago I was in a meeting in Singapore, hosted by the Chinese government there. We talked about MedDRA ICH initiatives and the like.

[Slide]

As far as what is going on at the MSSO this year and in the near future, originally MedDRA was available just in English and Japanese. In 2002 it has been translated into French, German, Portuguese and Spanish down to the PT level, the preferred term level. Spanish is down to the LLT level. That is still finishing its quality review because there are so many terms there. There are translation issues based on the English MedDRA as far as British and American spelling conflicts when you have to have a unique translation for each term, let alone the use of synonyms. In other languages, they may have only two synonyms to our five. There is also the reverse, where they have

five or six synonyms to our one word. So, the LLTs are still being worked on. As of now, you can get MedDRA only in Portuguese and Spanish. The Germans have signed over their property rights to the EFPIA who is the trustee of MedDRA, but we have not received permission to distribute it. And, we are still waiting for the French to sign over their property rights.

As far as other languages, the only ones that we know that are actively being worked on is Greek. There have been discussions and indications that other languages have been started, but then we hear that they have been stopped again so I am not sure that we have anything for you on other languages at this point, other than that the Greeks hopes to be finished in 2003 with their translation.

All supporting documents that come with MedDRA, the user's manual, intro. guide, "what's new document," are also provided in translation to go with the distributed translation set.

[Slide]

MedDRA term selection--this is a plug for ICH. The MSSO provides support to the working group that helped create the ICH points to consider document for the use of MedDRA. It is posted on our website as well as the ICH website as of the meeting in September. The document was updated to deal with Version 5.0 of MedDRA which was the current version at that time.

[Slide]

Currently we are facing the near release of MedDRA 6.0 in early March. We have about 60 proposed complex changes. After review and comment, that was whittled down to 12, which was then posted again on the website for public comment. Based on the comments that came back from the subscribers, the implementation is ongoing right now to get ready for the March release.

We have also received direction from the management board to look at modified terms within MedDRA for at least aggravated, exacerbated and worsened for this release. The issue here is larger than what we can deal with actually. It

involves E2B being reopened and talking about modified field indicators. Most of the terms in MedDRA have multiple modifiers and there is a desire not to allow MedDRA to exponentially grow. So, if you have a disorder, you could have a disorder aggravated; you could have a disorder chronic; you could have a family history of this disorder.

So, EFPIA has put together a white paper that was also presented to the ICH and that is why they agreed to reopen the E2B committee to look at this, and also some other issues on harmonization. But for now, we have reviewed the PT levels for these three term modifiers to verify if there is a clear indication that there is no unique medical concept between it and the non-modified version.

Also, EMEA has put out a requirement for the use of MedDRA for the coding of investigator terms in E2B for their filings in Europe. We have received listings from both pharmaceutical companies as well as FP in Europe and we are in the process of implementing many of them. Again, the

clean-up of British/American spelling is going forward.

[Slide]

This is just a question, again based on client feedback, the subscriber base, about the growth of MedDRA. MedDRA itself will be saying they did X thousands of changes per release. The reality is that over the first four years of MedDRA's use there have only been 4000 terms added to MedDRA. There have been 20,000 changes to MedDRA but only 4000 new terms. MedDRA will continue to grow in spite of the stabilization effort because of things like the requirement to add investigator terms; the requirement to deal with some other things coming down the line here.

Also, the management board has requested that we do more actively to increase transparency of our process. So, we are in the process of augmenting our websites, more user groups. Right now we really only have one per region. There are several unofficial user groups that are going on through PhRMA, not through PhRMA but independently

and also through EFPIA. But we will also be sponsoring more MedDRA MSSO sponsored users.

The bottom line bullet here is NOS, modified terms and SSCs, again, there are more indications of issues still to be resolved, and once they are resolved they could impact the growth of MedDRA one way or the other, depending upon the management board's decision.

[Slide]

The current issue that is probably being talked about is the special search categories that were viewed, when they were created by the original expert working groups of ICH, as a means of doing data analysis of MedDRA-coded terms. But the comments here are from users as to why they don't use them: "They are too broad." "They are incomplete." The companies just build their own type of thing.

Back in the beginning of 2002, the MSSO itself took a look at the MedDRA and felt that there was a lack of a way of easily doing analysis using MedDRA. So, the MSSO created a proposal to

the management board, which is being reviewed, called the creation of MedDRA analytical groupings, which is taking the concept of the SSCs but adding a hierarchy to it and making them more specific and not so broad. I will have an example of that coming up.

In proposing this and formulating this proposal, we talked about it at many of our user groups; we talked about it at several conferences; and we have also talked about it with individuals in industry. Some of those individuals in industry and CIOMS think this is a great idea too and CIOMS now has an initiative to create what they are calling special search queries which--a funny thing--almost matches word for word ours. But we have been participating in the past two CIOMS meetings as invited guests to work out a relationship of how the MSSO group and the CIOMS group can work together to produce a single product for everybody which we think, and they think, is the proper thing to do, and not create disparate products that would add to confusion down the line.

[Slide]

This is just an idea of what is in the SSCs now as far as definitions of what we are calling the MedDRA analytical groupings.

[Slide]

This is a listing of the proposed MedDRA MAGs that we have developed already, the ones in red, QT prolongation being one of them. Again, when we went to the CIOMS meetings, their list almost matches ours about 80 percent. They are working on the same topics we are. So, we are following forward on that.

[Slide]

This, again, is just to explain what I meant by the hierarchy. I was going fast because I was told I only had 15 minutes to talk and I wanted to be able to spend a little bit of time on this slide. If you were to try to do some analysis and you wanted to go to the blood lymphatic system to look at a specific issue, you could do a very broad scope query of bone marrow toxicity, or you could go down through the MAG hierarchy to look at the

thrombocytopenia, the leukopenia, or you may want to go even further down to granulocytosis type of query. So, you can have a very broad scope or a narrow scope. You can pick and choose how you want to use it for what type of analysis you need to do.

This is just a concept to help people understand what we are talking about when we are talking about analytical groupings and structure. It would not interfere with the basic MedDRA that is there. The basic MedDRA, based on feedback, seems to be in pretty good shape as far as doing data coding. When you want to find a term to code it, it is there. It is trying to take the term from here, and here, and here and pull it together and then produce some analytical results where there is a problem. Even NCI has created a whole set of neoplasm queries to do that, to link neck and head; to link all the different organs that are dealing with squamous cell as opposed to the way they are laid out for MedDRA coding purposes where it is by system, organ, class or by, you know, a specific infection or whatever.

That is the end of my quick speech. Thank you. Any questions? Yes, sir?

UMEN: We have been involved in preparing new drug applications, and one of the efforts of any new drug application is to get to the point of putting a label, a package insert, if you will, in the United States summary of product characteristics, in Europe and so on.

Many companies are now moving to using MedDRA in the pre-approval stages for their clinical trials as a method of coding adverse events. The transition from adverse events collected and coded under MedDRA to a package insert for purposes of labeling brings up some of the challenges that the special service categories or the MAGs begin to deal with. But MedDRA just is very problematic for use in getting to labeling even though for coding it has great value. The ultimate use of those codes is to enable analyses, at least in part as far as I see it, and to get the labeling.

I think the agency needs to coordinate its

thinking and its contribution to ICH for the challenge that MedDRA is presenting in getting to labeling terms in an NDA for the initial label and which also represents challenges for labeling updates.

REVELLE: I assume you are not waiting for a comment back; you are just making a statement.

UMEN: You haven't answered.

REVELLE: No, there is no answer. I have talked to people that have been involved in the original expert working groups in the early '90s, and they are split too as to whether you should be able to roll up things in MedDRA or easily extract them from MedDRA, and then you get the others, diametrically opposed, who say a label is a negotiated item between you and the regulator and it is like God's given right and it should not be tampered with by government. I have not heard of any requirements in any of the three ICH regions about labeling and MedDRA.

UMEN: I know MedDRA is not a requirement per se for the label but it is a tool--

REVELLE: It is a tool that could be made use of.

UMEN: And it is quite challenging.

REVELLE: Really, when we talked about the MAGs and how they could be developed, there is the potential, as you point out too, that somewhere down the line there might be a semi-solution that would help with the labeling things, and the signal detections and all the other things. Anybody else have a question or comment?

MOLZON: Is this a question that could at least be presented at the MedDRA management board meeting?

REVELLE: The MedDRA management board has talked about labeling and even there, I mean, the MedDRA management board is made up of ICH people so you have FDA, JPMA, WHO, PhRMA, JPMA and they are split too. I mean, there are certain hot buttons and when the topic comes up everybody polarizes to opposite sides. There are other places where they come together just like, earlier, talking about some of the ICH initiatives that were being worked

and certain ones that were easily worked, and those that nobody can bring up yet and labeling has been that way. Yes, I attend the management board meeting as the director of the MSSO. Andrea Fete and Miles Braun, from CBER and CDER, represent FDA at the management board as well. Any other questions?

[No response]

Thank you very much.

ANQUEZ: Thank you very much. Thank you very much, everybody on the panel, for their terrific presentation. We have now reached maybe the most important part of the meeting, which is to hear from you all and welcome your input. We did receive a request from Dr. Mooney to do a presentation so I will turn the floor over to him.

MOLZON: Could you just introduce yourself for the transcript?

Presentation and Comments

MOONEY: Hi. I am Pat Mooney, from Eli Lilly Company. I am the team leader for the group at Lilly that has been working on the CTD

implementation at Lilly. As such, we have gone through and looked at all the summaries that have to be prepared for the CTD.

[Slide]

What we have here is a request for additional CTD guidance. Whether that guidance comes from ICH or from FDA, we would like to have additional guidance as to how to prepare some of the additional summaries. What we propose is a structured approach to integrated clinical summaries, and by integrated clinical summaries we include the integrated safety summary and efficacy summary that we already prepare for the FDA as one of those kind of integrated clinical summaries/analyses, and also integrated with that structural approach, the individual study reports because some elements of the study reports could also be integrated into the structured approach.

We would like to avoid building in unnecessary redundancy in the data analyses in the clinical overview summary, integrated summary of effectiveness and integrated summary of safety. A

lot of the data elements, as you will see, are the same and it doesn't make sense to keep saying the same thing over, and over, and over again in the different documents. We feel like this would provide the reviewers a framework for the region specific safety and effectiveness reviews. It does not mean they would all review their dossiers the same way but there would be a framework on which they could hang their review process.

[Slide]

I did not provide an actual pyramid here but we view this, as Justina did earlier, that this is really a pyramid of summaries and then getting down into the data. These are quotes directly from the guidances that exist:

The clinical overview is intended to provide a critical analysis of the clinical data in the Common Technical Document.

The summary, the CS, is intended to provide a detailed, factual summarization of the clinical information in the CTD.

The ISE, the integrated summary of

effectiveness, should provide an integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication.

The ISS, the integrated summary of safety, is, in part, simply a summation of data from individual studies and, in part, a new analysis. We understand that but it goes beyond what can be done with individual studies.

[Slide]

At Lilly, we have gone through this process of looking at the ISS/ISE and the CS, as well as the CO, clinical overview to see how they compare and we have actually mapped the different sections of the CS, the CO, the ISS and the ISE to see how the different elements correlate. We think that there is a very large overlap between the ISS and ISE and the clinical summary.

Now, the size of this overlap, in the first part of the slide, is fairly general but what we see is that there is actually more overlap there than what we are led to believe sometimes in some of the things that we hear. In particular the ISE,

we feel that it is pretty much covered by the elements of the efficacy summary within the CS. For the ISS, most of the data elements and data integrated analyses for that are also included in the CS and the safety summary of the CS, although dropouts aren't really covered as well in the CS as they would be by the ISS.

[Slide]

Having said that, here is an example of a document that we have prepared. We go by the table of contents from the 1988 guidance from FDA and correlate that with the actual content of that guidance versus the content of the CTD guidance for the safety and the efficacy summaries.

[Slide]

Now, proposed structure--like I said before, we feel that either ICH or FDA should provide clarity around the clinical summaries. We view that the current FDA advice on ISS has been a series of PowerPoint presentations and really isn't adequate to really tell us exactly what to do here in industry.

What we propose is almost a restatement of what is in the guidance already but we really would like to go beyond that. The clinical overview, section 2.5, is a detailed critical analysis and interpretation of the meaning of the efficacy and the safety data. That is basically what it said in the guidance. The clinical summary is an integrated factual analysis and presentation of the efficacy and safety data. It doesn't go into saying this is what it means; it just says these are the facts and these are the integrated facts across studies.

What would go into module 5, section 5.3.5.3, which is a place to put the ISS and the ISE, for the ISE we would say that it is basically optional since it is basically covered by the efficacy section of the CS. However, if we need to discuss efficacy that didn't pan out, that is where we could put that or other analyses that might add hundreds or thousands of pages that we would not want to try to shoe-horn into the CS.

With the ISS, as I said, presentation of

specified additional and integrated analyses that is specified by either FDA as guidance or by ICH as "here's where you put this." Also, patient narratives and we know there is not enough room in the CS for all the patient narratives, and also special safety analyses that might be requested by the agency at the time of getting guidance prior to the submission, so like in a pre-NDA conference for example. There you go. Thank you.

MOLZON: I could add, as I mentioned in my presentation, that there is a series of questions and answers for the safety, efficacy, quality and electronic submission in general and we are in the process of discussing putting together a question and answer section specifically for the ISS and ISE because there is so much confusion.

MOONEY: And we will probably be contributing to that.

MOLZON: Right. So, I would like to actually take your presentation with me to ICH if you could e-mail it to me.

MOONEY: I will give you my copy.

MOLZON: Okay. As I said before, originally we were going to rewrite the ISS and the ISE as a stand-alone document and then the PDUFA-3 risk management topics overtook it. So, we are in the process of figuring out how to make all these things fit together.

MOONEY: I could also send you that actual document that I showed you one page of.

MOLZON: Yes, thank you very much. Because the more practical information we have, the better. Thank you.

MOONEY: Thank you.

UMEN: This subject has come up, as you know, multiple times. It has been at meetings you and I have participated in before at DIA. I think there is enough experience now amongst companies in writing ISS, ISE and now CTDs, including the summaries and the overviews, that we should perhaps contemplate either a session at the annual meeting, which we might have scheduled at DIA, or a special workshop, much like the one you had last week on QT, because this is a very hot topic and I think

you would get a lot more than can be handled in just an hour. There would be some real airing of the challenges and the overlaps that really bear on what the last presenter just discussed. It is a hot topic.

MOLZON: The slide presentations that Dr. Mooney mentioned were actually Dr. Temple's presentation at the last annual meeting in Chicago. As you said, now that people have more experience they basically have a better understanding of how this all fits together, and we really should take advantage of all that experience. When we were writing this, you know, it was twenty people or less in a room. We really need the practical experience to see how all this fits. What we are trying to do is not reopen the document but, with this question and answer system that we have established in ICH, to clarify some of the issues. Those questions represent consensus responses. So, in fact, hopefully, it would provide clarity on what the intent was of those documents.

But I think Bob Temple might also be

presenting this again at the DIA annual meeting in San Antonio. That, of course, is in June, right before July.

ANQUEZ: Thank you very much, Patrick, for that presentation and thank you all for your comments and questions.

MOLZON: You can either do it from here or there, whatever is easiest.

Presentation and Comments

UMEN: I am very happy to do it from here. Michael Umen, Michael Umen and Company. I made a submission for the docket to the agency earlier today and by e-mail earlier this week.

I speak on behalf of Michael Umen and Company. We are a private company, over twenty years old, dedicated to producing drug documents for use in the registration of human pharmaceuticals.

I come here today because I think it is important at this stage to make the agency aware, and certainly the public including all the involved constituencies, that just like drugs are subject to

patents and the patent laws of the United States and other countries, and intellectual property laws in general, so are systems used in producing drug documents subject to U.S. patents and patents in other countries of the world. I am aware of four such patents. We are the patentees. The numbers of those patents, for the record, are 5-734-883; another is 5-963-967; a third is 6-205-455; and, finally, 6-505-218, the last of which was just awarded about two weeks ago.

The reason I bring it to your attention is because the patents cover methods that are applicable to producing drug documents, including those covered by the eCTD. I am really very much of the opinion that our intellectual property rights and those of other inventors here should be respected, just as intellectual property rights are being respected by ICH in the context of the MSSO for MedDRA. So, I have submitted copies of our patents to the public record.

Just so you are aware, patentees are afforded the right to exclude others from making,

using, offering for sale or selling the patented claims in the United States for U.S. patents, and similarly in other parts of the world. That includes patents that claim drug document production systems. I would not want to see a situation arise where legal action has to be brought to stop companies from producing the drug documents that go into their next submission, or stop FDA from reviewing an NDA or BLA simply because the agency is using a system that infringes a valid U.S. patent.

So, I bring it to your attention. I ask the agency to look carefully at this. I wish to notify the public that these patents exist and respectfully request that our intellectual property rights be respected here. Thank you.

MOLZON: Michael, what I am going to do with the patent you gave me is introduce it to the ICH steering committee so everyone is aware and we can, you know, determine next steps.

UMEN: Thank you.

ANQUEZ: Thank you, Michael. Any

questions or requests to speak? If not, I think we will bring the meeting to a close and, once again, I would like to thank all of you for coming here in spite of the weather to give us your input. It is very important. We value it. Thank you very much.

[Whereupon, at 1:20 p.m., the proceedings were adjourned.]

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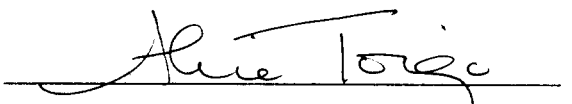
CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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